FREQUENTLY ASKED QUESTIONS

ISSUE 1

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This FAQ is supplemental to the FAQ page on the XPRIZE Healthspan website at www.xprize.org/prizes/healthspan/faq and made available for competing teams on www.pop.xprize.org/prizes/healthspan/resources. Additional FAQ issues will be released as the competition progresses.

GENERAL COMPETITION INFORMATION

1. **What is the Intent to Compete Application?**
   The Registration Form (formerly labeled as the Intent to Compete Form) is a required activity that all teams interested in competing in XPRIZE Healthspan must complete on the POP (Prize Operations Platform; www.pop.xprize.org) before they can pay the competition's registration fee. The questions in this Registration Form is for XPRIZE to understand the general characteristics of interested teams, and is used for preliminary informational purposes only.

   Starting from the public announcement and launch of XPRIZE Healthspan (along with the FSHD Bonus Prize) in November 2023, the competition has been in a Pre-Registration phase through July 30, 2024 to review Public Comment on the Preliminary Competition Guidelines, engage with and recruit interested teams, and other activities to promote the competition. On July 31, 2024 Primary Registration for the competition opened with new and updated resources made available for teams to progress in the registration process and prepare their Qualifying Submissions. For more details on the timeline progression of major events and milestones for XPRIZE Healthspan and the FSHD Bonus Prize, please review Table 2 in the Competition Guidelines.

2. **How will I be updated about changes to the guidelines?**
   The most updated version of the Competition Guidelines will always be available on our website at www.xprize.org/prizes/healthspan/guidelines and also saved in POP at www.pop.xprize.org/prizes/healthspan/resources. The latest posted version of the Competition Guidelines will always supersede any previous versions released.

3. **What information is needed for the Qualifying Submission and how is it judged?**
   The Qualifying Submission includes the proposed therapeutic background and rationale, supporting evidence, safety assessment, team qualifications, clinical center quality, regulatory approval ability, and early-stage clinical testing plans.

   Completed Qualifying Submissions will be reviewed for scientific and technical merit by an independent Judging Panel, who will assign a weighted score based on specific criteria. A detailed description of submission components and judging criteria is located in the Qualifying Submissions guidance documents on www.xprize.org/prizes/healthspan/resources. Please note that separate submissions are required for XPRIZE Healthspan and FSHD Bonus Prize (depending on which, or both, competition tracks a team chooses to enter in).

4. **Are interventions that are based on informatics, predictive personal health insights and digital therapeutics considered appropriate for this competition?**
   Yes. Teams with these types of technologies will need to adequately describe their approach in the qualifying submissions so that the Judging Panel understands what and how it will be implemented in trials and hopefully scaled post-prize. The finals' trial design and Grand Prize awarding will be based on individuals meeting personalized response thresholds, not mean treatment / control group comparison. This was born out of n-of-1 medicine and person-centered care.

   For more information on eligible therapeutic treatments as defined for this competition, refer to "Therapeutic Treatments" in Section 9 of the Competition Guidelines.

5. **Can more than one team win the prize?**
   We anticipate awarding only the best team to surpass the pre-determined thresholds. However XPRIZE will defer to the independent Judging Panel for all final adjudication of the Grand Prize Winner or Winners in the unlikely event that the judges determine that more than one team equally surpasses the highest threshold.

6. **What happens if no one wins the prize?**
   If the Judging Panel decides not to award any amount of the Prize Purses, the remaining money will be returned to the Co-Title Sponsor(s). This applies to both the prize purses pertaining to XPRIZE Healthspan as well as the FSHD Bonus Prize.

7. **I am unable to pay the registration fee. Are there any fee discounts or waivers available?**
   XPRIZE will review a team's eligibility for a reduced or fully waived fee on a case-by-base basis. Generally, eligibility for a consideration of financial difficulty only applies to teams that have either of the following: a not-for-profit status, are a mostly student-led team based within an academic institution, or the team is geographically based in a LMIC (Low and

Middle-Income Country). To request for a fee discount or waiver, the Team's Lead Point of Contact must submit a request to healthspan@xprize.org, providing sufficient explanation for why they qualify. XPRIZE reserves the right to deny any requests based on insufficient or non-eligible reasons.

8. **Can minors compete in this competition?**
   Minors are welcome to join existing XPRIZE Healthspan Teams or form a Team, as long as they provide written and signed consent of a parent or legal guardian. The parent or legal guardian must also sign any other forms and waivers required by the Competition on their behalf.

TESTING & JUDGING

9. **How do I advance to the Semi-Finals of XPRIZE Healthspan? Does the team need to perform original research or can they use existing literature as evidence to devise a treatment protocol?**
   The first step in advancing to Semi-Finals is to submit a Qualifying Submission Application by December 20th, 2024. The Qualifying Submission Application instructions can be found at www.xprize.org/prizes/healthspan/resources.

   The purpose of the Qualifying Submission Application is for the competing teams to demonstrate their likelihood of success in the subsequent Semi-Finals and Finals rounds. Teams can think of the Qualifying Submission as a "roadmap" of their plan for the testing of their therapeutic in early state proof of concept trials. In the Qualifying Submission, teams must submit information on their therapeutic solution, proof that the therapeutic is considered safe (or is under consideration by a regulatory body), evidence that the therapeutic effects relevant endpoints/biomarkers, a safety assessment, and a description of their study team and clinical center, among other things. Please read the Application instructions carefully and reach out to the Healthspan Team if you have any questions. Judges who review the Qualifying Submission Applications should be able to clearly determine if the team has the necessary qualifications, partners (e.g., clinical centers), and sufficient supporting evidence for use of their therapeutic. Up to 40 teams will be chosen as Semi-Finalists.

   Please note that for the FSHD Bonus Prize, up to the top 8 teams will be selected to receive a Milestone Award and designated as Finalists of this bonus competition track. There will not be a Semi-Final round for the FHSD Bonus Prize; however, the deadline for completing Qualifying Submissions is the same as the XPRIZE Healthspan track (December 20, 2024).

10. **How do I advance to the Finals?**

Teams that advance to the Semi-Final round will be expected to execute their proposed plans for early-stage trials as they describe their Qualifying Submission Application, incorporating feedback from judges, regulators, or oversight committees as needed. Teams will propose their own study design, endpoints and assessment measures needed, and criteria used to support go / no-go decisions. During the Semi-Finals term, teams are expected to engage the clinical center that will be used in Finals and conduct a small study (~30-60 days with 5-20 people receiving the therapeutic treatment) to demonstrate likelihood of successful completion of a 1-year clinical trial in Finals. Teams will be responsible for submitting regulatory and human subjects safety approvals, engaging a clinical center for testing, acquiring and administering the therapeutic solution, collecting and managing data, and submitting reports to XPRIZE. Semi-Finals trials should also provide evidence that it will be feasible to enroll and retain participants meeting their Inclusion and Exclusion Criteria. Following judging, up to 10 teams will be chosen as Finalists.

11. **When are we expected to go to clinical trials? When do the one-year trials / Finals start?**
    Teams must complete small, early stage proof-of-concept trials for Semi-Finals. We expect these trials to start in Q2 2025 and conclude by Q2 2026 (all data submitted for judging). We expect the one-year Finals trials to begin in late-2026 and conclude by December 2029, with all data submitted for judging by February 2030.

12. **Will XPRIZE Healthspan provide teams some estimates of expected testing costs?**
    No. It is the responsibility of teams to complete their own budget projections. If teams require assistance, we recommend that they reach out to consultants. However, XPRIZE will cover certain subsets of laboratory assay costs for the Finals round only. Any biospecimen that the team is required to collect for judging will be shipped to a central lab and the cost of performing the assay will be covered by XPRIZE.

CLINICAL TRIAL AND THERAPEUTIC DESIGN

13. **What types of clinical trial designs are allowed?**
    For Semi-Finals, we leave the design of the trial up to the discretion of the competing team.

    For XPRIZE Healthspan Finals, all teams *must* use a single-crossover controlled trial design with personalized response thresholds. This design permits determination of the effect of a therapeutic solution within a study participant and is robust to high heterogeneity of effect, non-ideal conditions, and differing participant characteristics that will be encountered in the prize. This is a before / after intervention experimental clinical study design with a single cross-over that consists of a 3 month baseline period and 1-year intervention window (15-month total time from recruitment and initial testing to follow-up per participant).

The XPRIZE FSHD Bonus prize Finals are suggested but not required to use this trial design, but must justify the study design, total time from recruitment to follow-up, and sample size used.

14. What types of therapeutic solutions are allowed?

Therapeutic solution categories can refer to the following, but the list is not exhaustive. If you have questions about whether your therapeutic is acceptable, please contact the XPRIZE Healthspan team.

- Medicinal drugs - can be investigational new drugs or repurposed drugs or medicines already prescribed for other indications
- Biologics - such as vaccines, immune modulators, monoclonal antibodies, blood and blood components, allergenics, and recombinant protein therapeutics
- Devices - such as novel medical therapeutic devices, game-based devices, digital health devices, and devices to deliver specific exposures
- Gene and cell-based therapies
- Electroceuticals and magneceuticals
- Nutritional supplements and nutraceuticals
- Dietary or lifestyle intervention approaches
- Other innovative interventions
- Varied combinations of the above

15. Do I need my own Institutional Review Board (IRB)?

Yes, teams will need to secure their own IRB approval for their trials, both for Semi-Finals and Finals.

16. How will data be collected for this competition? Can I use my own data collection platform?

For the Semi-Finals, teams will collect their data using the data collection platform of their choice. We strongly recommend a HIPAA (or international equivalent, e.g., GDPR) compliant Electronic Data Capture (EDC) system.

Finalist teams will be expected to use common clinical protocols and enter data that will be used for judging of the competition into the XPRIZE Healthspan central data collection and management system maintained by the XPRIZE Healthspan Data Coordinating Center (DCC). Teams can use their own EDC systems to collect additional information.

17. Is biospecimen collection required?

Yes, biospecimen-based biomarkers must be collected for Finals. Specific assays will be decided upon in 2026, but teams should expect to collect samples (e.g., plasma, serum,

whole blood, urine and saliva) on a schedule reflective of the Finals clinical trial design: a screening visit, 3 baseline visits, a midpoint visit, and 3 follow-up visits.

Collection procedures must be performed by trained phlebotomy personnel provided by the teams' Clinical Centers using universal precautions and training in venipuncture collection techniques recommended by the XPRIZE Central Lab.

18. What endpoints will be used in the finals competition?

The main outcome for Grand Prize adjudication is operationalized as the within-person change in assessments of muscle, cognitive, and immune function relative to baseline. Each functional domain will be evaluated based on a set of appropriately validated assessment measures. Awards will be indexed against the expected 10 year, 15 year, and 20 year declines in established referent populations for each domain. The tables below are reposted from Section 9: "Finals Testing Outcomes and Endpoints" of the Competition Guidelines, that show optimal and acceptable measures. Final decisions on endpoints and thresholds for awarding will be made prior to the start of Finals in 2026.

MUSCLE FUNCTION

Subdomain	Type	Optimal Measure	Acceptable Measure
Endurance Capacity	Function	Cardiopulmonary Exercise Test (peak VO_2)[32]	• 6-min Walk Distance[33] • 400m Walk Time[34]
Lower Body Power	Function	Knee Extensor Power or rate of torque development (RTD)[35]	• 1-Repetition Maximum[36]
Muscle Mass	Biospecimen or Imaging	Urinary D3 Creatine Dilution[37, 38]	• CT muscle volume[39, 40] • MRI muscle volume[38]
Muscle Summary Score – exceed threshold for % improvement in 2 out of 3 measures			

COGNITIVE FUNCTION

Subdomain	Type	Optimal Measure	Acceptable Measure
Cognitive Summary Score	Function	NIH Toolbox Fluid Composite (executive function, attention and processing speed, working memory)[41, 42]	CanTab / Cambridge Cognition (executive function, attention and processing speed, memory)[43]
Cognitive Summary Score – exceed threshold for % Fluid Cognition Composite OR improvements in >50% of selected cognitive function tests **NOTE: Additional tests could be named.** Tests of mood and sensory perception are under consideration. We will also continue surveillance of blood-based biofluid based biomarkers of cognitive function; should these be clinically validated during the prize window they will be measured by XPRIZE-determined central or regional laboratories.			

IMMUNE FUNCTION

Subdomain	Type	Optimal Measure	Acceptable Measure
Response to challenge	Biospecimen	*Ex vivo* naïve immune response to a new stimulus (e.g. yellow fever)[44]	Cellular mediated antigen-specific immune response in stimulated PBMCs[45] or response to vaccine[46]
Immune cell composition	Biospecimen	IMM-AGE Score[47]	CD4+ : CD8+ ratio and lymphocyte : neutrophil ratio
Inflammatory status	Biospecimen	'Multikine' multiplexed assays (e.g. SASP Index)[48, 49, 50]	
Immune Summary Score – exceed threshold for % improvement in 2 out of 3 measures. **NOTE: IMMUNE ASSAYS LISTED ARE NOT FINAL.** Example assays to be performed centrally by XPRIZE Healthspan contracted laboratories are provided above. Biospecimen based immune function biomarkers will be analyzed centrally at XPRIZE determined laboratory facilities, and we will prioritize standardized collection and banking of peripheral blood mononuclear cells, plasma, serum, and whole blood. XPRIZE will announce specific assays and response thresholds prior to measurement and judging.			

19. Does the therapeutic treatment need to show a change in all three domains?

Yes. The therapeutic treatment must exceed threshold for % improvement in 2 out of 3 muscle measures, exceed threshold for % Fluid Cognition Composite OR improvements in >50% of selected cognitive function tests, AND exceed threshold for % improvement in 2 out of 3 measures.

20. Who is responsible for monitoring the safety of participants?

Safety is paramount for XPRIZE Healthspan. It is the responsibility of teams to monitor safety of participants. Each Competing Team's Team Lead will have primary responsibility for the safety of participants as it relates to their study protocol, and good clinical practice which includes local safeguards related to Covid-19 or other infectious disease.

The Competing Team will engage their own Data and Safety Monitoring Committee or similar study monitoring committee according to their local regulations. For example, a team competing in the United States will be required to have their own Institutional Review Board (IRB) assigned to their clinical trial. This committee / board will have responsibility for monitoring study data for evidence of adverse events attributable to participation in clinical trials. Reports from this committee will be submitted for judging as part of the XPRIZE Healthspan Competition. Clinical Site monitoring by XPRIZE may be conducted to ensure that the rights and well-being of human subjects are protected.

Safety data will be regularly monitored by the Competing Teams and their regulatory and safety oversight committees to identify any issues related to participant safety and trial conduct. This includes adherence to safety alert protocols set by the teams.

INCLUSION & ENROLLMENT

21. Are there specific diversity requirements for participant enrollment?

Participant recruitment targets should strive for balance in sex (ideally, 50% female, but 40-60% balance is acceptable with accommodation for intersex individuals) and also ethnic and racial composition reflective of the geographic region from which recruitment will occur. Teams should proactively incorporate best practices to build diverse and inclusive research participant recruitment strategies, and XPRIZE will actively seek additional support to incentivize diversity.

22. Why was the age-range for clinical studies adjusted from 65-80 to 50-80?

Our selected age-range is 50-80 years for participant eligibility in XPRIZE Healthspan as well as FSHD Bonus Prize Finals. Though several advisors suggest restricting the age-range to make it easier to compare effects across teams (e.g. 70-80 years), we opted to allow a 30-year window. This allows teams maximum flexibility to define the characteristics of their population, which may in turn improve generalizability and drive innovation in defining best populations and context of use for gerotherapeutics.

- *Lower Age Limit:* We have lowered the allowable age from 65 years to 50 years based on feedback from potential teams and key stakeholders. There is a strong interest in the field of longevity and use of gerotherapeutics in persons aged 50-70 years, especially those who may already demonstrate evidence of lower functional capacity, clinical risk factors, or other biologic age acceleration. However, teams are cautioned that a younger-aged and high functioning population challenge the ability to demonstrate sufficient improvements in one year to meet required thresholds for awarding.
- *Upper Age Limit:* The upper age limit of 80 is included in our guidelines based on referent data needed to assign response thresholds for grand prize awarding. Based on preliminary data from the Baltimore Longitudinal Study on Aging provided by our advisors (published report pending*), the change in function over time is quasi-linear until age 80. After age 80, the change is more variable and accelerated. Though of strong interest to develop therapeutics for those over 80 years, it was not recommended for this competition.

23. Treatments for 50-60 may not be effective at 70-80 and the other way around. Will this be prevented by requiring distribution of ages at 70 ?

Therapeutics may have differential physiologic effects in persons aged 50 vs. 80 years. This is not disputed, and the pharmacokinetics and pharmacodynamics of their drug, or age-dependent physiologic effects of their therapeutic approach must be considered carefully by teams.

- *Prize Model.* The prize model is fundamentally different from running a single trial. We opted to remove constraints on teams to allow greater generalizability and innovation, but

maintain rigor of testing validation. The teams need to demonstrate major therapeutic effects in their selected population aged 50-80 years to win. But how they do so is up to the teams and their selected therapeutic, provided standards of safety and ethics are met.

- *New Design & Personalized Response Thresholds.* The within-person percent improvement and personalized response thresholding for success makes the prize more robust against differences in populations. However, it may be more challenging for a therapeutic to meet thresholds for improvement if a population that is too young / healthy is selected.

REGULATORY & LEGAL

24. Do teams need their own regulatory approvals?

Yes, teams need appropriate regulatory approvals from the country or countries in which they intend to run their clinical trials.

25. Do all teams need to go through the FDA for an IND?

As above, teams need appropriate regulatory approvals from the country or countries in which they intend to run their clinical trials. Should the team's therapeutic require an Investigational New Drug (IND) application from the Food and Drug Administration (FDA) in the United States, (or equivalent through European Medicines Agency, etc.), then it is the responsibility of the team to seek regulatory consult, submit an application for a pre-IND, or seek an exemption.

26. Can a US-based team run a trial in another country?

Yes, as long as they abide by regulations in each country.

27. Our team has not established a formal legal entity such as a company or LLC. Would XPRIZE help facilitate the process of legally forming a team?

XPRIZE will not provide services. However, over the lifetime of this competition, if there is someone in our partnership ecosystem that is capable of providing consultation or counsel in these types of issues, we will provide the names and contact information of these ecosystem partners that are available for teams to hire.

28. Are individual team members personally subject to the Competitor Agreement or is only the corporate entity that is the team?

No, it is just the legal entity who takes on any liability.

29. Once trials are complete, will the team have regulatory approval to sell and commercialize the therapeutic?

Participation in the competition does not automatically give teams regulatory approval to sell and commercialize their product; XPRIZE is not a regulatory agency and competing or winning the grand prize is not equivalent to an indication for use or commercialization

FUNDING & INVESTMENT

30. Does XPRIZE provide financial support to competing Teams?

XPRIZE does not provide direct financial support to Teams during or after the competition, aside from the prize purses awarded by the independent Judging Panel. However, XPRIZE strives to support the Teams throughout the competition by bringing competitors together to share ideas, encouraging collaboration among teams, and more generally, supporting innovation by building an ecosystem of strategic partnerships and industry allies, including: innovators, engineers, scientists, entrepreneurs, potential funders, media and marketing professionals.

31. How can I find funding for my Team?

There are many ways for Teams to look for funding. XPRIZE will strive to highlight Teams in the media and, when appropriate, provide guidance to Teams on how to promote themselves; this is a benefit of competing in an XPRIZE and has helped previous competitors to gain attention from the public and potential investors. Teams from previous competitions have also successfully used crowdsourcing websites to assist with fundraising. Additionally, there are Milestone Awards that teams can earn during the Semi-Finals and Finals rounds of the competition.

We do not favor any one Team; therefore, we do not provide specific connections or funds to individual Teams.